

REMARKS

Claims 1, 2, 5-8 and 22 were pending. Claims 2, 5 and 7 are cancelled by this amendment.

Claim 1 has been amended to incorporate the limitations of claim 2 that the first light and heavy chain pair is expressed at a different time than the second light and heavy chain pair is expressed and that both the first light and heavy pair and the second light and heavy chain pair are expressed by the same cell.

Claim 6 has been amended to improve clarity and dependency.

Claim 8 has been amended to improve clarity with regard to the nature of the bispecific antibody and to amend dependency.

Claim 22 has been amended to improve clarity.

No new matter has been introduced by the amendments.

Specification

Applicant has amended the specification as requested by the Examiner.

Claim Objections

The Examiner objected to claims 5-8 for depending from non-elected claims. Applicant has cancelled claims 5 and 7. Claims 6 and 8 have been amended to depend from claim 1.

Applicant's amendment to claim 22 corrects the spelling error noted by the Examiner. would have modified the prior art in the manner claimed must be set forth. *Id.* at 1741.

Rejections Under 35 U.S.C. §112, second paragraph

The Examiner rejected claims 1, 2 5-8 and 22 as indefinite. Applicant addresses the rejection of each claim below.

Claims 1 and 5-8 (essential steps or elements)

The Examiner argued that claim 1 omits essential steps or elements. Referring to claim 1, the Examiner stated that it was unclear how contact between certain light and heavy chain pairs

was inhibited. Applicants have amended claim 1 to delete this limitation and incorporate limitations of claim 2. Thus, the method of claim 1 entails "expressing in a cell a first light chain and a first heavy chain at one time and expressing in the same cell a second light chain and a second heavy chain at a different time". In this manner the formation of undesired light and heavy chain pairs is inhibited. Claims 2, 5 and 7 have been cancelled. Claims 8 and 22 have been amended to depend from claim 1.

Claims 5-8 ("the first and the second H chain" and "the first and the second L chain")

The Examiner argued that there was insufficient antecedent basis for the phrases "the first and the second H chain" and "the first and the second L chain" in claim 5. Claim 5 has been cancelled as has claim 7. Claim 8 had been amended to depend from claim 1 and does not include the objected to phrases.

Claim 7 ("the first pairs or the second pairs")

The Examiner argued that there was insufficient antecedent basis for the phrase "the first pairs or the second pairs" in claim 7. Claim 7 has been cancelled.

Claims 2, 5-8 and 22 ("a first pair and a second pair of the antibody")

The Examiner argued that the phrase "a first pair and a second pair of the antibody" in claim 2 is indefinite. Claim 2 has been cancelled as have claims 5 and 7. Claims 8 and 22 have been amended to depend from claim 1 and their includes the objected to phrases.

Claim 22 (essential elements)

The Examiner argued that claim 22 omits essential elements. In particular, the Examiner stated that the structural relationships between the various vectors, chains and promoters are missing.

Applicant has amended claim 22 to specify that "expression of the first light chain and the first heavy chain are under the control of a first expression regulator and the expression of the second light chain and the second heavy chain are under the control of a second expression regulator and the first and the second expression regulators are different". Further, claim 22 has been amended to specify that either: (a) the first light and heavy chains are expressed by the same vector as the second light and heavy chains or (b) the first light and heavy chains are

expressed by the different vector than the second light and heavy chains. Applicant believes that claim 22 as amended does not omit essential elements.

In view of the forgoing, Applicant respectfully requests that the rejections under 35 U.S.C. §112, second paragraph be withdrawn.

Rejections Under 35 U.S.C. §103

The Examiner rejected claims 1, 2, 5-8 and 22 as obvious in view of Carter et al. ("Carter"; *J Immunol Methods* 248:7, 2001) in view of Peipp et al. ("Peipp"; *Biochem Soc Trans* 30:507, 2002) and Shalaby et al. ("Shalaby"; *J Exp Med* 175:217, 1992). According to the Examiner, Carter expresses a heavy and light chain pair recognizing one antigen in the same cell as a different heavy and light chain pair recognizing a different antigen wherein the knobs-in-holes technique is used to promote the association of pairs required to form a bispecific antibody. Peipp describes various methods for producing bispecific antibodies. According to the Examiner, Peipp and Shalaby describe expressing the V region of a heavy and a light chain recognizing one antigen in one *E. coli* strain and separately expressing V region of a heavy and light chain recognizing a different antigen in a different *E. coli* strain.¹ The separately expressed halves of the bispecific antibody are purified from the respective *E. coli* strains and chemically linked. The Examiner argued that it would have been obvious to modify the method of Carter by using the separate expression methods of Peipp and Shalaby thereby arriving at the presently claimed methods.

Applicant disagrees with the Examiner's analysis.

The Supreme Court recently clarified that for an invention to be obvious under § 103, the factors set forth in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966) must be considered, including an analysis of the scope and content of the prior art and the differences between the claimed subject matter and the prior art. See *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct.

¹ Applicant does not believe that Peipp explicitly discloses this approach. Rather Peipp reviews various methods for producing bispecific antibodies.

1727, 1739 (2007). Importantly, an explicit rationale for why one having ordinary skill in the art would have modified the prior art in the manner claimed must be set forth. *Id.* at 1741.

First, one would not have been motivated to modify Carter using the teaching of Shalaby because Shalaby uses *E. coli* for expression. As Peipp explains, difficult refolding of larger antibody chains is difficult in bacterial expression systems. Peipp goes on to say that production in *E. coli* "is most commonly used for the diabody format, while short chain bispecific antibodies are preferentially expressed in mammalian cells". Because Carter's knob-in-hole method depends on pairing between heavy chain constant regions and because Carter uses full-length heavy chains, Carter's method is not suited to the bacterial expression methods of Shalaby because Peipp suggests that such antibodies cannot be effectively produced in *E. coli*. Thus, one seeking to improve Carter would not even consider the methods of Shalaby and Peipp.

Second, even if one were motivated to modify the method of Carter using the methods of the Shalaby or Peipp one would arrive not at the currently claimed methods, but rather at a method in which a light chain and a heavy chain having a modified Fc for knobs-and-holes was expressed in one cell line and a different light chain and a different heavy chain having a modified Fc for knobs-and-holes was expressed in another cell line. One would not arrive at the presently claimed methods which require temporally separated expression in a single cell line. There is nothing in the cited references to suggest modifying the method of Carter, with or without the knob-in-holes modifications, to achieve temporally separated expression in a single cell rather than expression in different cells.

Finally, there is nothing in the cited references to suggest that the presently claimed methods would be useful for generating bispecific antibodies. The art, for example, Carter, teaches the expression of two different pairs of heavy and light chains in the same cell leads to unwanted chain pairings. There is nothing to suggest that temporal separation of expression could solve this problem. Even when there is temporal separation of expression, all four chains are present in the same cell at the same time because the pair of chains produced first are, of course, still present when the pair of chains produced second are produced. Carter explicitly teaches that expression of all four chains in the same cell leads to the formation of nine, different

undesirable pairings as well as the one, desirable pairing. Thus, one could not have a reasonable expectation of success in the preparation of antibodies by the method of the current claims.

In view of the forgoing, Applicant respectfully requests that the rejection of the pending claims as obvious in view of Carter, Peipp and Shalaby be withdrawn.

The Examiner rejected claims 1, 2, 5-8 and 22 as obvious in view of Ridgeway et al. ("Ridgeway"; *Protein Engineering* 9:617, 1996) in view of Peipp et al. ("Peipp"; *Biochem Soc Trans* 30:507, 2002) and Shalaby et al. ("Shalaby"; *J Exp Med* 175:217, 1992). The Examiner argues that the claims 1, 2, 5-8 and 22 are obvious in view of Ridgeway, Peipp and Shalaby for essentially the same reason the Examiner argued that these claims are obvious in view of Carter, Peipp and Shalaby. Indeed, the knobs-in-holes method used by Ridgeway is very similar to that of Carter. The Examiner's position that claims 1, 2, 5-8 and 22 are obvious in view of Ridgeway, Peipp and Shalaby is incorrect for the same reasons that the Examiner's position that the claims are obvious in view of Carter, Peipp and Shalaby is incorrect.

In view of the forgoing, Applicant respectfully requests that the rejection of the pending claims as obvious in view of Ridgeway, Peipp and Shalaby be withdrawn.

Conclusion

Based on the foregoing, the Applicants believes that the rejections have been overcome. It is respectfully submitted that the application should be found in condition for allowance, and an early notice toward that end is earnestly solicited.

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Respectfully submitted,

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